

What is claimed is:

1. An isolated nucleic acid molecule comprising the sequence as set forth in any one of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 8, SEQ ID NO: 9,
5 SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, or SEQ ID NO: 13, or a portion of any one of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, or SEQ ID NO: 13.
- 10 2. A recombination vector for replacing an Ig gene segment from a non-human animal with a human Ig gene segment, comprising from 5' to 3', a 5' nucleotide sequence, said human Ig gene segment, and a 3' nucleotide sequence, wherein said 5' nucleotide sequence and said 3' nucleotide sequence are homologous to the 5' and 3' flanking sequences of said Ig gene segment from the non-human animal.
- 15 3. The recombination vector of claim 2, wherein said non-human animal is an animal which relies primarily on gene conversion in generating antibody diversity.
4. The recombination vector of claim 3, wherein said animal is rabbit, pig, chicken,
20 sheep or cow.
5. The recombination vector of claim 3, wherein the Ig gene segment from a non-human animal is a gene segment coding for a heavy chain or light chain constant region.
- 25 6. The recombination vector of claim 5, wherein said vector comprises from 5' to 3', a 5' nucleotide sequence as set forth in any one of SEQ ID NO: 12, SEQ ID NO: 13, a portion of SEQ ID NO: 12, or a portion of SEQ ID NO: 13; a human heavy chain constant region gene segment; a 3' nucleotide sequence as set forth in SEQ

ID NO: 10 or a portion of or SEQ ID NO: 10; and wherein said vector is useful for replacing a rabbit heavy chain constant region gene segment.

7. The recombination vector of claim 5, comprising the nucleotide sequence as set forth in SEQ ID NO: 51 wherein said vector is useful for replacing a rabbit heavy chain constant region gene segment.

8. The recombination vector of claim 5, wherein said vector is useful for replacing a rabbit light chain constant region gene and comprises a nucleotide sequence as set forth in SEQ ID NO: 53.

9. The recombination vector of claim 5, wherein said vector is useful for replacing a chicken light chain constant region gene and comprises a nucleotide sequence as set forth in SEQ ID NO: 57.

10. The recombination vector of claim 3, wherein the Ig gene segment from a non-human animal is a gene segment coding for a heavy chain or light chain variable region.

11. The recombination vector of claim 10, wherein said vector is useful for replacing a rabbit heavy chain variable region gene and comprises a nucleotide sequence as set forth in SEQ ID NO: 52.

12. The recombination vector of claim 10, wherein said vector is useful for replacing a rabbit light chain variable region gene and comprises a nucleotide sequence as set forth in SEQ ID NO: 54.

13. A transgenic vector comprising a humanized Ig locus, wherein said humanized Ig locus is derived from an Ig locus or a portion of an Ig locus of a non-human animal and comprises multiple Ig gene segments wherein at least one of said gene

segments is a human Ig gene segment, wherein said gene segments are juxtaposed in an unrearranged, partially rearranged or fully rearranged configuration, and wherein said humanized Ig locus is capable of undergoing gene conversion and producing a repertoire of humanized immunoglobulins in said non-human animal.

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14. The transgenic vector of claim 13, wherein said non-human animal is an animal which generates antibody diversity substantially by gene conversion.

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15. The transgenic vector of claim 14, wherein said non-human animal is rabbit, pig, chicken, sheep or cow.

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16. The transgenic vector of claim 13, wherein said humanized Ig locus is a heavy chain locus and comprises at least one V gene segment, at least one D gene segment, at least one J gene segment and at least one constant region gene segment.

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17. The transgenic vector of claim 16, wherein said constant region gene segment is a human heavy chain constant region gene segment.

18. The transgenic vector of claim 17, wherein said human heavy chain constant region gene segment is a C γ .

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19. The transgenic vector of claim 17, comprising about 10-100 V gene segments and at least one human V gene segment, wherein said human V gene segment is placed downstream to said 10-100 V gene segments.

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20. The transgenic vector of claim 19, wherein said V gene segments are selected from V gene segments at the 3' V-region of said non-human animal and human V gene segments.

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gene segment is linked to the sequences of non-human origin operably as to permit gene rearrangement and gene conversion of said humanized Ig locus and the production of a functional repertoire of humanized antibodies in said non-human animal.

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28. The method of claim 27, wherein the integration of said human Ig gene segment is achieved by homologous recombination, thereby replacing an Ig gene segment in said Ig locus or said portion thereof from said non-human animal.

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29. The method of claim 28, wherein the homologous recombination is achieved in a bacterial cell, a yeast cell, or a non-human animal cell.

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30. The method of claim 28, wherein the human Ig gene segment is provided on a recombination vector, and is linked to a 5' nucleotide sequence and a 3' nucleotide sequence which are homologous to the 5' and 3' flanking sequences of said Ig gene segment from the non-human animal.

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31. A transgenic animal comprising a humanized Ig locus, wherein said humanized Ig locus is derived from an Ig locus or a portion of an Ig locus of a non-human animal and comprises multiple Ig gene segments wherein at least one of said gene segments is a human Ig gene segment, said gene segments being juxtaposed in an unrearranged, partially rearranged or fully rearranged configuration, and wherein said humanized Ig locus is capable of undergoing gene conversion and producing a repertoire of humanized immunoglobulins in said non-human animal.

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32. The transgenic animal of claim 31, wherein said animal is selected from rabbit, pig, chicken, sheep or cow.

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33. A B cell from the transgenic animal of claim 31.

34. A method of making a transgenic non-human animal capable of producing a functional repertoire of humanized Ig heavy chains, comprising:

- (i) introducing a transgenic construct according to claim 16 into a recipient cell of a non-human animal and integrating the humanized heavy chain locus in the transgenic construct into the genome of said recipient cell; and
- (ii) deriving an animal from the recipient cell having the humanized heavy chain locus integrated in the genome, thereby producing a functional repertoire of humanized Ig heavy chains.

35. The method of claim 34, wherein said animal is rabbit and said recipient cell is a cell in an early embryo.

36. The method of claim 35, wherein said rabbit has an impaired expression of endogenous Ig molecules.

37. The method of claim 34, wherein said animal is chicken and said recipient cell is a fertilized egg.

38. The method of claim 37, wherein said chicken has an impaired expression of endogenous Ig molecules.

39. A method of making a transgenic non-human animal capable of producing a functional repertoire of humanized Ig light chains, comprising:

- (i) introducing a transgenic construct according to claim 21 into a recipient cell of a non-human animal and integrating the humanized light chain locus in the transgenic construct into the genome of said non-human animal; and

- (ii) deriving an animal from the recipient cell having the humanized light locus integrated in the genome, thereby producing a functional repertoire of humanized Ig light chains.

5 40. The method of claim 39, wherein said animal is rabbit and said recipient cell is a cell in an early embryo.

41. The method of claim 40, wherein said rabbit has an impaired expression of endogenous Ig molecules.

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42. The method of claim 39, wherein said animal is chicken and said recipient cell is a fertilized egg.

43. The method of claim 42, wherein said chicken has an impaired expression of endogenous Ig molecules.

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44. A method of making a transgenic non-human animal capable of producing a functional repertoire of humanized antibodies, comprising:

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- (i) introducing a transgenic construct according to claim 16 and a transgenic construct according claim 20 into a recipient cell of a non-human animal, and integrating the humanized Ig loci in the transgenes into the genome of said non-human animal; and
- (ii) deriving an animal from the recipient cell having the humanized Ig loci integrated in the genome, thereby producing a functional repertoire of humanized antibodies.

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45. A method of making a transgenic non-human animal capable of producing a functional repertoire of humanized antibodies, comprising

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- (i) making a transgenic non-human animal capable of producing a functional repertoire of humanized heavy chains;

- (ii) making a transgenic non-human animal capable of producing a functional repertoire of humanized light chains; and
 - (iii) mating the transgenic non-human animal of (i) with the transgenic animal of (ii); and
 - 5 (iv) selecting an offspring which produces both humanized heavy chains and humanized light chains thereby obtaining a transgenic non-human animal capable of producing a functional repertoire of humanized antibodies.
- 10 46. A humanized immunoglobulin produced using the transgenic animal of claim 31.
47. A humanized immunoglobulin derived from a transgenic animal, comprising at least a portion of a human immunoglobulin polypeptide sequence.
- 15 48. The humanized immunoglobulin of claim 47, wherein said transgenic animal generates antibody diversity by gene conversion and/or hypermutation
49. The humanized immunoglobulin of claim 48, wherein said transgenic animal is a rabbit, chicken, sheep or cow.
- 20 50. The humanized immunoglobulin of claim 49, wherein said human immunoglobulin polypeptide sequence is a heavy chain or light chain polypeptide sequence.
51. The humanized immunoglobulin of claim 50, wherein said portion of a human immunoglobulin polypeptide sequence is a human constant region polypeptide sequence.
- 25 52. The humanized immunoglobulin of claim 51, wherein said human constant region polypeptide sequence is C γ , C κ , or C λ .
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53. The humanized immunoglobulin of claim 51, wherein said portion of a human immunoglobulin polypeptide sequence further comprising a human V domain polypeptide sequence.
- 5 54. The humanized immunoglobulin of claim 47, wherein said humanized immunoglobulin is specific for an antigen.
55. The humanized immunoglobulin of claim 54, wherein said antigen is a microorganism selected from bacterium, fungus, or virus; an antigenic portion of
10 said organism; an antigenic molecule derived from said microorganism; or a tumor-associated antigen.
56. The humanized immunoglobulin of claim 55, wherein said bacterim is selected from *S. aureus*, *Pseudomonas aeruginosa*, enterococcus, enterobacter, or
15 *Klebsiella pneumoniae*.
57. The humanized immunoglobulin of claim 55, wherein said fungus is selected from *Candida albicans*, *Candida parapsilosis*, *Candida tropicalis*, or *Cryptococcus neoformans*.
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58. The humanized immunoglobulin of claim 55, wherein said virus is selected from respiratory syncytial virus (RSV), Hepatitis C virus (HCV), Hepatits B virus (HBV), cytomegalovirus (CMV), EBV, or HSV.
- 25 59. The humanized immunoglobulin of claim 55, wherein said antigen is selected from Her-2-neu antigen, CD20, CD22, CD53, prostate specific membrane antigen (PMSA), or 17-1A molecule.
- 30 60. An antibody preparation, comprising the humanized immunoglobulin of any one of claims 46-48.

61. The antibody preparation of claim 60, wherein said preparation is a monoclonal antibody preparation.

5 62. The antibody preparation of claim 60, wherein said preparation is a polyclonal antibody preparation.

63. The antibody preparation of claim 62, wherein said preparation is substantially non-immunogenic to human.

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64. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and the antibody preparation of claim 60.

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65. A method of treating a disease in a human subject comprising administering to said subject a thereapeutically effective amount of the antibody preparation of claim 60.

66. The method of claim 59, wherein said disease is caused by bacterial, fungal or viral infection, or said disease is a cancer.

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